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**European Perspectives in Cardiology.Funding: Human Frontier Science Program**

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## European Perspectives

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# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

## European Perspectives in Cardiology



### Spotlight: Philippe Purnode, MD



**“If the ATP Test Is Positive in a Patient Who Has Syncope of Unknown Origin, We Implant a Pacemaker”**

**Philippe Purnode, MD, cardiologist, Arrhythmia Unit of Brussels Heart Center, St. John Clinic, Brussels, Belgium, external consultant cardiologist, Arrhythmia Unit, Université Catholique de Louvain (UCL) Mont-Godinne Clinic, Yvoir, Belgium, and past-president of the Young Cardiologists' Club, talks to Monika Polak, PhD.**

Thirty percent of syncope cases are of unknown cause, even after a complete diagnostic workup. However, a recent article in *Circulation* suggests that adenosine triphosphate (ATP) testing has a role in helping decide which patients with syncope of unknown origin might benefit from active dual-chamber pacing.<sup>1</sup> The authors go on to say that current European guidelines on syncope of unknown origin,<sup>2</sup> which suggest that use of the ATP test should remain under investigation, should now be revisited.

Philippe Purnode, MD, external consultant cardiologist in the Arrhythmia Unit, Université Catholique de Louvain (UCL) Mont-Godinne Clinic, Yvoir, Belgium, and cardiologist in the Arrhythmia Unit of Brussels Heart Center, St. John Clinic, specialises in rhythm electrophysiology and was involved in the study. He says he has been using the ATP test routinely in his clinical practice for some time.

Dr Purnode explains, “In my practice, we usually use the test to see whether a patient needs to be implanted with a pacemaker. If the ATP test is positive (when we have an asystole >10 seconds), we implant a pacemaker.”

In the study, 80 patients (mean age 76 years) with syncope of unknown origin and atrioventricular/sinoatrial block >10 seconds under ATP administration had a programmable pacemaker implanted. They were randomised to either active pacing (dual-chamber pacing at 70 bpm) or backup pacing (atrial pacing at 30

bpm; control) and followed for up to 5 years (mean 16 months). Syncope recurred in 21 percent of those receiving active pacing compared with 66 percent of patients receiving backup pacing (hazard ratio 0.25). Dr Purnode says these results are comparable to those he sees in everyday practice.

**“We Started a Programme to Ablate the Pulmonary Vein at My Hospital 2 Years Ago”**

Dr Purnode's path into medicine and the decision to study at UCL was in part influenced by his father, an endocrinologist, who had studied medicine at UCL. The proximity to his home, ≈10 km away, also made it “very easy” to study there. However, he did not follow his father into endocrinology. He explains, “I am interested in the physiology of the cardiac muscle. My professor who taught cardiac physiology made it sound amazing. That was at the beginning. I then wanted to do all my work in the cardiac field.”

Dr Purnode completed his medical degree at UCL in 1995 and trained as a specialist in internal medicine at UCL from 1995 to 1998. He then trained as a specialist in cardiology from 1995 to 2002, working as a clinical assistant in a variety of hospital clinics throughout this period. In 2002, he was awarded first prize in internal medicine at UCL for “cardiac resynchronisation therapy.” Also in 2002, he took

#### On other pages...



#### Funding: Human Frontier Science Program

Scientists who have used Human Frontier Science Program awards for cardiovascular research describe the award and their research. **Page f118**



*Dr Purnode (right) with his mentor, Professor De Roy (left), and the nursing team in the electrophysiology lab, Brussels Heart Center. Photograph courtesy of Dr Purnode.*

up his present appointments of external consultant cardiologist in the Arrhythmia Unit, UCL Mont-Godinne Clinic, and cardiologist in the Arrhythmia Unit of Brussels Heart Center, St. John Clinic.

Dr Purnode's move into electrophysiology was driven by Professor Luc De Roy, MD, one of the coauthors of the *Circulation* study, who in 2002 was also based at UCL Mont-Godinne. Under the guidance of Professor De Roy, Dr Purnode learned more about arrhythmias, performing electrophysiological studies and controlling implantable cardioverter-defibrillators and pacemakers. He also participated in numerous international, multicentre trials, although the ATP study is his first article in a peer-reviewed journal. He explains that when he was working as a fellow in Professor De Roy's Arrhythmia Unit, Professor De Roy asked him to carry out the ATP test as part of the study

collaboration. Dr Purnode says, "Professor De Roy was a good teacher and always has something good to say when we look at an electrocardiogram with a problem." The 2 continue to collaborate, sharing opinions on heart physiology, heart disease, arrhythmias, and electrophysiology. Dr Purnode has also been involved in developing atrial fibrillation ablation therapy at the Brussels Heart Center, St. John Clinic. He says, "We started a programme to ablate the pulmonary vein at my hospital 2 years ago, and I asked Professor De Roy to help us. Everything is going well now. I think we have a good collaboration with him, and I hope we can continue for a long time." At Brussels Heart Center, St. John Clinic, Dr Purnode works with electrophysiologists Peter Goethals, MD, and Gaetano Paparella MD, as well as Professor De Roy.

Dr Purnode's work at the Brussels Heart Center, St. John Clinic takes up 80 percent of his time (the other 20 percent being spent at UCL Mont-Godinne). He is focused on developing the Arrhythmia Unit and says, "I have plans to do more with arrhythmia and aim to treat people with arrhythmia problems correctly. That's my goal." Treating patients is the most important aspect of his work, and he finds the pulmonary vein ablation procedure particularly rewarding.

#### **The Young Cardiologists' Club: A Forum for "Sharing Opinion With Other Young Cardiologists About the Best Ways to Treat Patients"**

In 2006, Dr Purnode became secretary of the Young Cardiologists' Club (see [www.ycc.cardionet.be](http://www.ycc.cardionet.be)), a working group of the Belgian Society of Cardiology for cardiologists working or training in Belgium who are <40 years of age, which, Dr Purnode explains, "is all about sharing opinion with other young cardiologists about the best ways to treat patients." He held the post for 2 years before



*Dr Purnode with his colleague Dr Goethals, the current secretary of the Belgian Heart Rhythm Association. Photograph courtesy of Dr Purnode.*





*The Young Cardiologists' Club on a social event with their families. The club is a working group of the Belgian Society of Cardiology for cardiologists <40 years of age who are working or training in Belgium and "is all about sharing opinion with other young cardiologists about the best ways to treat patients." Dr Purnode was president of the club from 2008 to 2010. Photograph courtesy of Dr Purnode.*

becoming president, from 2008 to 2010. He adds, "In the club, we have people from the Dutch part and the French part."

Founded in 1991, the Young Cardiologists' Club is free to join and aims to provide young cardiologists with an opportunity to meet colleagues from other regions, and to use this forum to express and develop new ideas in cardiology. It is run by 4 board members—2 joint presidents (1 representing the French part of Belgium and 1 representing the Dutch part), who also sit on the board of the Belgian Society of Cardiology as representatives for the Young Cardiologists' Club, a treasurer, and a secretary. The current presidents are Antoine Guedes, MD, who is based at UCL Mont-Godinne, and Nico Van De Veire, MD, of Mary Mediatrix General Hospital, Ghent, Belgium.

The Young Cardiologists' Club also organises meetings. As well as its quarterly meetings, during which attendees discuss various issues or dilemmas relating to the treatment of cardiac disease that they have encountered and draw other members' attention to findings from recently published studies that they feel are particularly important, the club organises an annual symposium (mainly the responsibility of the presidents) to which international speakers are invited. Previous topics have included sexual dysfunction due to cardiac disease and uncommon cardiomyopathy. This year's symposium, to be held on October 20 at the Van der Valk Airport Hotel in Brussels, is titled "A Heart for Sports: Screening and Guidance for Patients." Speakers will include Professor Sanjay Sharma, MD, consultant cardiologist at St. George's Healthcare NHS Trust, London, England, and Andre La Gerche, MD, a cardiologist at St Vincent's Hospital in Melbourne, Australia.

In early spring each year, the Young Cardiologists' Club holds a 3-hour "ECG Course for Dummies," during which young cardiologists are shown ECGs depicting arrhythmias and asked to discuss the findings and present a "solution."

The Young Cardiologists' Club also organises purely social weekend events for members and their families and participates in occasional projects and initiatives. For example, in 2007, in collaboration with a host of other Belgian organisations, including the Belgian Society of Cardiology, the Young Cardiologists' Club was involved in a public education campaign on the recognition of the early signs of acute myocardial infarction, which involved developing posters, leaflets, and a website aimed at the general public.

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*Monika Polak is a freelance medical journalist.*

# Funding: Human Frontier Science Program

## Supporting Innovative Basic Research into Fundamental Biological Problems

Scientists who have used Human Frontier Science Program awards for cardiovascular research describe the award and their research to Jennifer Taylor, BSc, MSc, MPhil.

Based in Strasbourg, France, the Human Frontier Science Program (HFSP) supports innovative basic research into fundamental biological problems with an emphasis placed on novel approaches that involve scientific exchanges across national and disciplinary boundaries.

### Postdoctoral Long-Term Fellows

The HFSP awards international postdoctoral fellowships for basic research training. These awards are aimed at scientists with a PhD in a biological discipline to enable them to embark on a new project in a different field of the life sciences. Preference is given to applicants who propose an original study in biology that marks a departure from their previous PhD or postdoctoral work.



**Kaaweh Molawi, PhD,**  
postdoctoral fellow, Lab for  
Stem Cell and Macrophage  
Biology of Michael Sieweke,  
PhD, Centre d'Immunologie  
Marseille-Luminy,  
Marseille, France

Dr Molawi was awarded an HFSP long-term fellowship in 2011. The 3-year grant started in 2012 and covers his salary and funds for research and travelling. Together with Dr Sieweke, Dr Molawi aims to delineate the subtype-specific functions of monocytes and macrophages during cardiac tissue regeneration. The project is being conducted in collaboration with the lab of Nadia Rosenthal, PhD. Dr Molawi says, "The goal of this analysis is to modulate the response of monocytes/ macrophages in a proregenerative direction and to improve functional tissue regeneration."

The researchers will take advantage of self-renewing MafB/c-Maf double-deficient (Maf-DKO) macrophages that have recently been developed and described by Dr Sieweke's lab. "Maf-DKO macrophages can be amplified in culture without tumorigenic transformation while maintaining functional macrophage identity," explains Dr Molawi. "Therefore these cells represent an ideal tool to examine and manipulate monocyte/macrophage function in the context of tissue regeneration." The use of Maf-DKO cells for factor delivery or for novel monocyte-mediated cellular treatment strategies as an attractive alternative to stem cell-based cell replacement therapies will also be explored.

Before moving to Marseille, Dr Molawi worked at the Max Planck Institute for Infection Biology in Berlin, Germany, on the contribution of microglia-mediated inflammation during neurodegeneration. He says, "This work triggered my interest in the differential roles of myeloid cells in degenerative processes and tissue regeneration."



**Suphansa Sawamiphak,**  
PhD, postdoctoral fellow,  
Professor Didier Stainier's  
Lab, University of California,  
San Francisco, CA

Dr Sawamiphak received her HFSP long-term fellowship in May 2011. She says, "The fellowship provides me with not only a living and research allowance for 3 years, but also a great opportunity to join

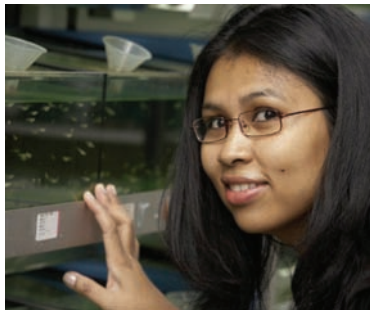
Professor Stainier's lab in a resourceful working environment at the University of California, San Francisco."

Previously, Dr Sawamiphak's PhD study at Johann Wolfgang Goethe University in Frankfurt, Germany, aimed to elucidate the entwined network of signal transduction that might bridge nerve wiring and sprouting angiogenesis. Using various techniques to assess angiogenic sprouting at the cellular and molecular levels, she found that the outgrowth of filopodial processes extended from specialised tip cells that leads the directional migration of vascular sprouts depends on ephrinB2, a well-known axonal guidance cue. EphrinB2 acts in concert with the most prominent angiogenic receptor, vascular endothelial growth factor receptor 2, to stimulate its endocytosis and thereby fine-tune its downstream signalling required for the migratory response of the endothelial tip cell. A similar mechanism is also involved in cancer vascularisation.

"The funding I have received from the fellowship allows me to pursue my interest in biomedical research as well as acquire experience with a different model organism to study human diseases," says Dr Sawamiphak. She is currently using zebrafish as a model system in a study aimed at identifying novel cellular and molecular players underlying the cross-talk between inflammatory response and cardiac growth and regeneration. To this end, she has been taking advantage of many attributes of the zebrafish, including powerful genetic tools, body transparency suitable for in vivo imaging, and anatomical similarity with higher vertebrates. She says, "My ultimate goal is a better



understanding of the developmental and restorative programme of the cardiovascular system to provide new approaches to treat the diseased heart.”



**Mirana Ramialison, PhD, postdoctoral fellow, Professor Richard Harvey's Lab, Victor Chang Cardiac Research Institute, Developmental Biology Division, Sydney, Australia**

Dr Ramialison began her 3-year HFSP long-term fellowship in February 2011. The fellowship covers her salary and provides a travel allowance. As a bioinformatician, Dr Ramialison's main focus of research is to model cardiac gene regulatory networks. She has also implemented the zebrafish model system in the lab to experimentally validate the predictions generated by the bioinformatics analysis. “I joined a multidisciplinary team of bioinformaticians and molecular biologists to successfully reconstruct the gene regulatory network driven by several cardiac transcription factors in a wild-type and disease context,” she says. “Through the bioinformatics predictions, we have discovered novel genes implicated in heart development and unraveled novel concepts in disease mechanisms.”

Dr Ramialison's previous research at the Developmental Biology Unit, European Molecular Biology Lab, Heidelberg, Germany, was mainly focused on establishing bioinformatics databases and tools to analyse the regulation of synexpression groups during development. She also examined specific synexpression groups using the medaka fish as a model system.



Photo courtesy of David Ausserhofer.  
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**Daniela Panáková, PhD, junior group leader, Max Delbrück Center for Molecular Medicine, Berlin-Buch, Germany**  
Dr Panáková held a HFSP long-term fellowship from 2008 to 2011. It provided living expenses and a research and travel allowance to study the coordination of early embryonic function and patterning of the vertebrate ventricle in the group of Calum MacRae, MD, PhD, at Harvard Medical School and Brigham and Women's Hospital, Boston, MA. They discovered that the patterning of the gradient of electrical coupling requires noncanonical Wnt signalling and demonstrated that Wnt11 modulates electrical coupling through negative regulation of L-type  $\text{Ca}^{2+}$  channel conductance. Previously, as a PhD student in the lab of Suzanne Eaton, PhD, at the Max Planck Institute of

Molecular Cell Biology and Genetics in Dresden, Germany, Dr Panáková studied morphogen trafficking of the lipid-linked morphogens Wingless and Hedgehog. It had been proposed that these morphogens are transported over long distances in the developing epithelia on particles termed argosomes. “We were able to show that *Drosophila* lipoprotein particles associate with Wingless, Hedgehog, and a number of GPI-linked proteins,” says Dr Panáková. “We proposed that lipoprotein particles act as vehicles for their long-distance movement and are required for Wingless and Hedgehog long-range signalling.”

“In between my graduate studies and postdoctoral work, I moved to a different area of research (from cell and developmental biology to organogenesis and physiology) and changed model organisms and continents,” says Dr Panáková. “These are all assets required (among others) for receiving a HFSP fellowship.” Dr Panáková adds, “The travel allowance was instrumental in giving me flexibility to connect and network with other scientists.”

Dr Panáková received a Helmholtz Young Investigator Grant in 2010 and joined the Max Delbrück Center for Molecular Medicine in Berlin-Buch, Germany, as a junior group leader in 2011.

### Career Development Awards

The goal of HFSP Career Development Awards is to encourage former HFSP long-term and cross-disciplinary fellows to return to their home country to initiate an original research programme in their own labs as independent researchers. Candidates are encouraged to select research institutions other than their PhD institute to facilitate their scientific independence.



**Jan Huiskens, PhD, physicist, Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany**

Dr Huiskens leads a Max Planck research group that works on organogenesis in zebrafish with quantitative microscopy and image processing techniques. During his PhD, he developed an innovative fluorescence microscopy technique called selective plane illumination microscopy. “It turned out to be extremely useful for imaging the cardiovascular system in small vertebrates such as zebrafish,” he says. His postdoctoral work from 2005 to 2009 was primarily funded by a cross-disciplinary HFSP fellowship, which allowed him to optimise the technique and perform experiments on the function and morphogenesis of the zebrafish heart at the University of California, San Francisco, in the lab of Professor Didier Stainier, PhD. He and his colleagues were able to image fluctuating calcium in the intact heart with high spatial and temporal resolution and describe mechanisms of cardiac valve formation.

Selective plane illumination microscopy is not only ideal for imaging sensitive samples such as living embryos due to its speed and low phototoxicity, but it can also be combined with innovative sample manipulation techniques, eg, optogenetics. “My work at the University of California, San Francisco, culminated in the development of an optically controllable pacemaker in zebrafish,” says Dr Huisken. “Using patterned illumination in our light sheet microscope, we located the pacemaker and simulated tachycardia, bradycardia, atrioventricular blocks, and cardiac arrest.”

Dr Huisken joined the Max Planck Institute in Dresden in 2010 to continue working on the cardiovascular system in zebrafish using home-built microscopes. A 3-year HFSP Career Development Award is now supporting him to investigate the embryonic zebrafish vasculature. The aim is to create a detailed, dynamic atlas of the vasculature as a first step to describe and quantify wild-type development through high-resolution time-lapse image acquisition, image processing, segmentation, and quantification. The digital data are automatically annotated with blood flow direction and speed, vessel diameter, and their hierarchy, etc. “In a following step, this knowledge will be used to identify and numerically describe novel vascular mutants and quantify the effects of drugs,” he says. “The zebrafish can thereby act as a model of human diseases and their treatment.”



**Julien Vermot, PhD, group leader, Institute of Genetics and Molecular and Cellular Biology, Illkirch, France**

Discoveries in the roles of fluid forces during embryonic development led to Dr Vermot receiving an HFSP Career Development Award in July 2010. With his colleagues in the lab of Scott Fraser, PhD, at California Institute of Techno-

logy, Pasadena, CA, he developed noninvasive methods to probe flow in live embryos. First, they identified the flow forces involved in controlling valvulogenesis during heart development and a flow-responsive gene linking blood flow and valve morphogenesis. Second, mixing classical approaches in genetics with light imaging to address cilia-mediated flow during development, they found that manipulating cilia dynamics affects inner ear formation. The use of fast imaging, optical tweezer, and mathematical modelling, uncovered the mechanism of action of cilia during this process.

The award provides €220 000 over 3 years, and Dr Vermot is using it to run a lab, which includes 2 PhD students,

2 postdocs, 1 engineer, and 1 lab manager. Their goal is to address the physical stimuli and molecular mechanisms that specify cell responses to flow forces during cardiovascular development.

Dr Vermot's group is located at the Institute of Genetics and Molecular and Cellular Biology in Strasbourg, France, and uses multidisciplinary approaches to address biological blood flow functions during embryogenesis. “Moving blood is a necessity for proper cardiovascular development. We are particularly interested in understanding the relationship between blood flow forces and tissue organisation in the process of valvulogenesis and angiogenesis,” he says. “We really enjoy interacting with physicists, engineers, and mathematicians, as they help us develop new models, approaches, and hypotheses related to the numerous roles of blood flow during cardiovascular development.”



**Massimo Mattia Santoro, PhD, associate professor, University of Torino, Torino, Italy**

Dr Santoro received an HFSP Career Development Award in 2008. It provided 3 years of funding for salaries, instruments, and reagents/disposables, which enabled him to set up his own lab at the University of Torino. His lab

uses the zebrafish model system to identify new molecular mechanisms and pathways involved in the formation and maturation of blood vessels, particularly focusing on endothelial cells and vascular mural cells. Recently, they described vascular smooth muscle cells in the zebrafish during evolution, and they characterised, in collaboration with another lab, the role of cathepsin D during zebrafish development. They have developed new techniques to study microRNA functions in the cardiovascular system in zebrafish, and, in collaboration with Pascal Meier, MD, in London, England, they are further characterising the vertebrate cIAP gene.

“Before obtaining the Career Development Award, I had been working on cloning new zebrafish mutants with specific cardiovascular development defects,” says Dr Santoro. “I identified the tomato mutant, a null mutant of cIAP1 with specific apoptotic defects in endothelial cells. Later on, I was also involved in the characterisation of microRNA functions in the zebrafish cardiovascular system, in particular microRNA-126.”

*Jennifer Taylor is a freelance medical journalist.*

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